associated with a more favourable prognosis in many malignant diseases. Indeed, in breast cancer, tumours positive for bcl-2 often have oestrogen receptors and a more favourable prognosis. Oestrogen has been shown to be a positive regulator of bcl-2 gene expression in breast cancer cell lines.[7]

The pro-apoptotic protein bax is the most studied member of the bcl-2 family in cancer. Loss of bax function seems to be important in the pathogenesis of colorectal cancers.[8] In preclinical studies, induction of bax has been reported to restore sensitivity to drug and radiation induced apoptosis, whereas overexpression of bcl-2 has been shown to suppress apoptosis. However, the few clinical studies on the predictive value of bcl-2 family proteins in treatment of haematological malignancies or solid tumours have produced conflicting results.[5 9]

Inducing apoptosis

Several strategies have been tried to induce the apoptotic programme. The first approach was gene directed therapy to restore normal p53. Although the results have been interesting, refinement of the vectors and delivery concepts is needed. The first phase I pharmacokinetic study with bcl-2 antisense oligonucleotide (which effectively degrades messenger RNA) in patients with non-Hodgkin's lymphoma shows that the treatment is well tolerated.[10] However, only one patient showed objective response while 11 patients had stable disease, and in nine patients the cancer progressed.[10] These types of therapies, however, are likely to be more efficient when combined with chemotherapy or radiation, which triggers apoptosis. It might also be beneficial to combine pro-apoptotic treatment with anti-angiogenesis treatments as hypoxia has been shown to promote apoptosis.[11]

Tumour heterogeneity and clonal variability will provide an extra challenge for future investigations and successful treatments based on apoptosis. The factors in apoptotic pathways have opened a new exciting dimension in our understanding of how and when cancer treatments succeed or fail—this holds promise for better therapeutic strategies in the future.

Competing interests: JS has received fees for speaking, organising education, and consulting from Aventis Pharma. She also works as a medical adviser at Aventis Pharma, Finland. The Karolinska Institute has a formal research collaboration with Bristol Myers Squibb on pharmacogenomics, from which JB's research group benefit. JB has received reimbursement for attending and speaking at scientific meetings and symposiums from many pharmaceutical companies active in oncology. He has received fees for consulting from Pharmacia.

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Does apoptosis have a role in neurodegeneration?

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Cells within the central nervous system die during both acute and chronic neurodegenerative disorders. Since the morphological and biochemical features of apoptosis were first described, neuroscientists have been asking whether this cell death is due to apoptosis and whether elucidating the mechanisms of apoptosis can provide new treatment strategies for intractable diseases such as stroke, Alzheimer's disease, and Huntington's disease.

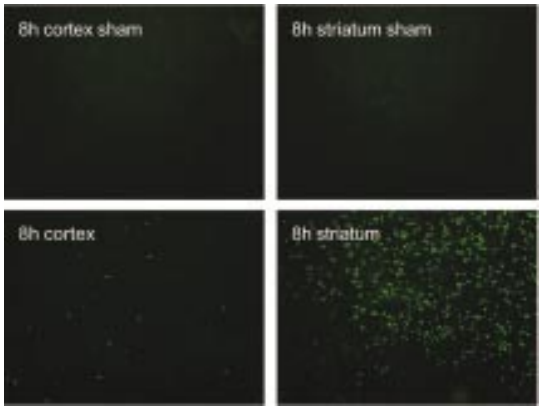
Detecting apoptosis

Much debate has ensued. Firstly, cell death in the central nervous system may not fit perfectly with our current classification of apoptosis and necrosis, which was defined using peripheral cells. Some of the methods used may not distinguish conclusively between apoptosis and necrosis. For example, transferase-mediated dUTP nick end labelling (TUNEL), a staining method that detects the broken ends of DNA within cells, is used to provide evidence of apoptosis. However, DNA can be fragmented in necrosis too.

Secondly, clinical symptoms may result from loss of neuronal function rather than apoptotic cell death. Many chronic neurodegenerative diseases are associated with intracellular aggregates of mutated proteins that cannot readily be disrupted, even by aggressive laboratory procedures. Such deposits may compromise neuronal function—for example, by blocking transport of nutrients along axons. A study of Huntington's disease in mice has shown that if generation of the mutant protein is halted, the aggregates are dissolved by the proteasome (the cellular machinery for removing unwanted proteins) and the neurological scores of the mice improve.[1] This suggests that, initially at least, symptoms may result from compromised neuronal function, with cell death having a subsequent role.

Supporting evidence

Evidence supporting a role for apoptosis in neurodegenerative diseases has come from studying rodent brain cells and by manipulation in animal models of



Cortex and striatum of rats eight hours after induction of permanent focal ischaemia by insertion of an intraluminal thread. Control animals (top) had sham surgery without ischaemia. Sections of brain were stained by transferase-mediated dUTP-biotin nick end labelling to detect broken ends of DNA. The sham controls show no TUNEL positive cells; sparse green staining (little cell death) is seen in the cortex, and extensive cell death can be seen in the striatum 8 hours after ischaemia

the levels of expression or activity of key molecules involved in apoptosis. Active caspases, the proteases activated during apoptosis, have been detected in dying neurones taken from patients with Alzheimer's disease. These enzymes can cleave β-amyloid, a protein implicated in the pathogenesis of Alzheimer's, generating a pro-apoptotic protein.[2] Furthermore, β-amyloid can induce apoptosis in cultured neurones,[3] but cells lacking caspases become resistant to β-amyloid. Similarly, although normal huntingtin, which when mutated caused Huntington's disease, is required for survival of neurones, mutant huntingtin can induce apoptosis of neurones.[4] Huntingtin can also be cleaved by caspases, and cleavage is enhanced by mutation of the protein.[5] Preventing cleavage by caspases reduces the toxicity of the mutant huntingtin. Such studies provide circumstantial evidence that apoptosis participates in chronic neurodegeneration.

Some of the best evidence for the role of apoptosis in neurodegeneration comes from studies of brain ischaemia or stroke (figure). Although necrosis predominates in the severely ischaemic core of injured tissue, apoptosis occurs in the less ischaemic region that surrounds the core.[6] Up regulation of several proteins that participate in apoptosis (for example, caspase-3) has been detected in stroke damaged brain tissue, and animals that have been engineered to overexpress anti-apoptotic proteins or that have been treated with caspase inhibitors show less damaged tissue after experimentally induced stroke.

The evidence therefore suggests that apoptosis has a role in neurodegeneration, and the studies described above highlight the possibility that pro-apoptotic agents such as caspases might be new targets for therapeutic intervention. Caspase inhibitors would seem especially applicable to situations of acute degeneration such as stroke. It remains to be seen whether they can also be used for slowly progressing chronic neurodegenerative conditions, where neuronal function may fail before cell death removes the damaged neurone.

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The healing touch

I read with fascination the *BMJ* article about the "patient friendly alarm system" in the last Christmas issue (2000;321:1565-6). For me it raised a memory; one that will remain evergreen.

Some years ago, on a wet sombre September afternoon, I responded to a persistent ringing on my front door bell. Aroused from a deep sleep, Kim, my Belgian shepherd dog, rushed to the door, his ears quivering alertly. I welcomed in a woman, whom I will call Christina. Thin, haggardly underweight, she sank speechlessly into an easy chair. A long silence followed. Eventually, in a barely audible voice, she told me that she had been recently widowed. Her husband, to whom she had been married for some 30 years, had collapsed and died while at work. Neither she nor her husband had been aware of any pre-existing health problems. Both had been eagerly planning to visit their married daughter in Australia. Silence followed. Time slowly passed as the distraught woman sank even more deeply into a world of darkness; her body stayed still while her head flopped loosely against her chest. She became oblivious to her surroundings, apparently deaf to any attempted conversation. There seemed no way for me to pierce the shell of suffering with which she had surrounded herself.

Would she, I wondered, follow her husband in her despair? Was there a real risk of suicide? How could I possibly ease her distress?

I turned to Kim, still snuggled by my side, gazing at him appealingly. Our eyes met. His response was swift. Rising, he silently positioned himself by Christina's unresponsive figure. Slowly he raised his forelegs to gently grasp her body, encircling her waist, and rested his head snugly on her lap, his eyes fixed on her. Slowly she lifted her head until her eyes met his. Tears trickled down her cheeks. She clasped his warm clinging body, and her lips stretched into a smile. Gently she stroked his head, and slowly her power of speech returned. Kim remained by her side, a loving presence.

My dog and I became listeners as words flowed at last. Christina joined us both in drink and food; before she left, she gave us her telephone number. In the weeks and months that followed, Kim remained her constant source of comfort and encouragement, her healing touch. That incident was, for me, not only an evergreen memory but also a lesson for life. I learnt to use my dog to help others in distress.

The power of healing does not lie solely in human hands.

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